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Editorial

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Challenges in biomolecular simulations

Inspired by the recent Simons Center for Computational Physical Chemistry Symposium at New York University on challenges in biomolecular simulations, we invited authors to contribute articles on the state of the art in biomolecular simulations, both current progress and anticipated challenges for the future. All areas of biomolecular modeling were welcomed, from quantum degrees of freedom to coarse-grained supramolecular complexes, bioinformatics, and machine learning. Of interest were contributions on algorithms, applications, and hardware implementations.

In the resulting special issue, many topics of modeling and applications are represented, spanning a large range of fascinating and important areas of multiscale modeling and simulation and chemical/physical/biological/biotechnological applications. The application systems encompassed a broad swath of the biomolecular universe, including antibodies, kinases, membrane complexes, posttranslational modifications, and protein-small molecule interactions. The studies offer key biophysical insights into the mechanisms of folding, recognition, binding, and phase transitions.

Two reviews by Bondar and Smith (1) and Smith et al. (2) define the state of the art of the area of bioenergetics. While the former outlines challenges in simulating proton motive force, namely, the electrochemical gradients needed for the generation of ATP molecules (1), the latter discusses how such energy currencies can be leveraged in the technology and manufacturing spaces to scale up the generation and assimilation of biological products and sustain the global economy (2).

Moving to original research articles, artificial intelligence (AI) in the biology revolution is reflected prominently in the special issue. Karolak and team (3) apply AI as a design tool to create new molecular structures by leveraging the strengths of transformers, graph neural networks, and variational autoencoders. Gerstein and co-workers (4) use AI in the context of a supervised on-the-fly dimensionality reduction method to drive molecular dynamics (MD) simulations.

Generalizable toolboxes offer another popular theme. For example, Monje and co-workers (5) present a Python-based toolbox for analyzing lipid membranes and biopolymers in molecular simulations, allowing users to compute and project biophysical properties onto a two-dimensional plane. Replica exchange transition interface sampling protocols are invoked by Ghysels and colleagues (6) for rare events in studying drug-protein interactions. A more integrated tool allowing high-throughput study of small molecule-protein interactions is offered by MacKerell and team (7), who combined computational hydrogen-deuterium exchange experiments with computational experiments, revealing previously unidentified "excipient sites" for therapeutic compounds. Gerstein and co-workers (4) developed a discard-and-restart MD simulation that optimizes the distance from targets to improve the performance of folding simulations by up to 2000-fold.

Applications include studying microtubule dynamics by using data-driven modeling, highlighting the generalizability of equation-free approaches (Voth and team (8)); chromatin unfolding dynamics combining bioinformatics with polymer modeling (Hilbert and team (9)); protein-glycan modeling using a novel workflow that integrates induced fit docking, molecular mechanics/generalized Born surface area binding free energy calculations, and binding pose metadynamics simulation (Li and Minkara (10)); neurotransmitter release mechanisms using coarse-grained MD simulations (Lindau and colleagues (11)); biophysical origins of circadian rhythms using a combination of biochemical assays, brute-force and accelerated MD simulations, and Markov state models with casein kinase (Partch and team (12)); phase-separation simulations of disordered proteins using hybrid coarse-grained and Folding@Home techniques and *in vitro* experiments, highlighting the role of aromatic amino acids in inducing order-disorder transition (Stelzl and co-workers (13)); MD simulations of how methylation affects the details of chromatin packing and promotes a range of molecular interactions (Schlick and team (14)); free energy simulations depicting how mutations of loops affect their receptor recognition, leading to disease outcomes (Juffer and colleagues (15)); and complexities underlying the nonelectrostatic and electrostatic origins of viscosity in concentrated antibody solutions (Lenhoff and colleagues (16)).

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Altogether, the special issue presents an objective view of the biophysics simulations and simulation-driven sciences to the community. It showcases both the strengths and weaknesses of multiple computational methods and applications and limitations across diverse systems. Most importantly, the articles collectively present a nuanced outlook on the needs and innovations in this ever-growing area.

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